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Antiarrhythmic drugs - The pharmacokinetic profile of some antiarrhythmic drugs is modified by abnormalities of cardiac output and regional blood flow after myocardial infarction, and this is especially relevant for drugs given repeatedly or by intravenous infusion; therefore measurement of antiarrhythmic drug concentrations is now increasingly used to regulate drug dosage. It may also be of value when arrhythmias fail to respond, or change unpredictably, when it is important to differentiate between lack of response due to inadequate dosage and aggravation or induction of an arrhythmia caused by drug toxicity.

Liver blood flow limits the rate of elimination of lignocaine,[9] and poor liver perfusion after myocardial infarction may cause drug accumulation if doses are too large. Optimal adjustment of lignocaine infusion rate will prevent cerebral toxicity and myocardial depression and this can be achieved by measurement of steady-state plasma concentrations. Ventricular arrhythmias are usually controlled by concentrations between 2 and 5 mg/l; higher concentrations are likely to result in toxicity, the risk rising with the concentration.[10]

About half of a dose of procainamide is excreted unchanged by the kidneys, and reduced renal function leads to accumulation when the drug is given repeatedly. Prevention of arrhythmias usually requires plasma concentrations between 4 and 8 mg/l with major toxicity beginning to occur above this range.[10]

Cinchonism and ventricular fibrillation due to quinidine are dose-related and can be prevented and diagnosed by measurement of the plasma quinidine concentration. Concentrations between 3 and 5 mg/l usually suppress arrhythmias; toxicity is increasingly likely at higher concentrations.[10]

Theophylline - Adverse reactions to the use of theophylline in bronchial asthma are almost always dose-related. Beneficial bronchodilator activity requires concentrations greater than 10 mg/l although concomitant use of β-adrenoceptor stimulants reduces the concentration required. Nausea and vomiting become common at 20 mg/l and intoxication is virtually certain at higher concentrations.[11]

Lithium - Because the therapeutic ratio of lithium is so low, plasma concentration measurements are mandatory to prevent toxicity. Where lithium is used in the prophylaxis of manic-depressive psychosis, twice-weekly estimations are recommended until the plasma concentration is between 0.8 and 1.0 mmol/l.[12] In subjects who are free from adverse effects and who remain unresponsive, the dose then can be safely increased to produce the optimum concentration of 1.2 mmol/l. For mania, high doses may be necessary from the outset and more frequent measurements are required. Strict timing of samples and of dosage during the 48 hours before sampling is advised to ensure that concentrations are comparable.

Even after initial dosage adjustment, impairment of renal function, concurrent diuretic therapy, a low-salt regimen or a reducing diet, pregnancy, or intercurrent infections can each raise the plasma concentration with resultant toxicity, which is confirmed if the plasma concentration exceeds 2 mmol/l and is likely between 1.5 and 2.0 mmol/l.[12]

Aminoglycoside antibiotics - Adequate bacteriocidal activity requires optimum peak plasma and tissue concentrations after each dose. Since aminoglycosides have half-lives which are considerably shorter than the

usual dosage interval, concentrations fall to very much lower 'trough' concentrations just before each dose. Ototoxicity is related both to the duration of treatment and to the mean trough concentration.[13]

When renal function is impaired, drug half-life is prolonged and modifications of maintenance dose and dosage interval are necessary to minimise the risk. Nomograms are available,[14 15] based upon age, body-weight, and plasma creatinine, as aids to both gentamicin and kanamycin dose calculations. The duration of therapy should still be kept as short as possible and dosage reviewed daily when renal function fluctuates. Peak (1 hour after dose) and trough (just before dose) concentrations should ideally be below 10 mg/l and 2 mg/l respectively for gentamicin and below 30 mg/l and 10 mg/l respectively for kanamycin to prevent ototoxicity.

The newer aminoglycosides appear to be less ototoxic but, even so, concentrations of tobramycin and sisomycin should be adjusted in the same way as those of gentamicin.[16] Amikacin and kanamycin also have similar toxic concentrations.[17]

Salicylates - When prescribing salicylates for long periods, the usual aim is to give the highest dosage that can be tolerated by the patient, reducing the doses if tinnitus should occur. However, salicylate elimination is saturable and concentrations may suddenly rise to unexpectedly high levels while the dose is being increased gradually. Moreover, tinnitus is related to plasma concentration only when hearing is normal. It is therefore advisable to titrate the dose according to the plasma concentration, aiming for the range (in adults) 250-300 mg/l.[18] Concentrations over 300 mg/l are associated with hyperventilation.

Tricyclic antidepressants - In patients with endogenous depression, sustained benefit from nortriptyline occurs when plasma concentrations are between 50 and 150 mg/l;[19] with higher concentrations response is poor for reasons which remain obscure. It is not clear whether this phenomenon occurs with other tricyclic compounds. Samples should be drawn 10-15 hours after a dose, since drug equilibration between plasma and tissues is slow. The suggested correlation between very high concentrations of any of these compounds and signs of cardiac toxicity requires general confirmation before routine measurement of drug concentrations can be recommended as a routine procedure in patients suffering from overdosage.

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